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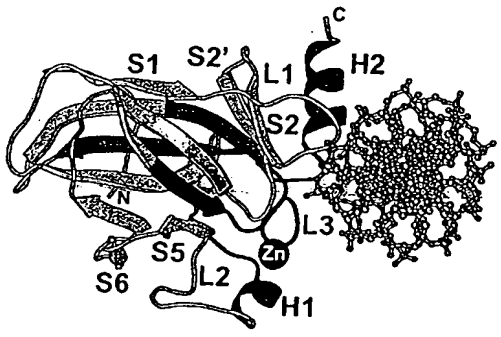
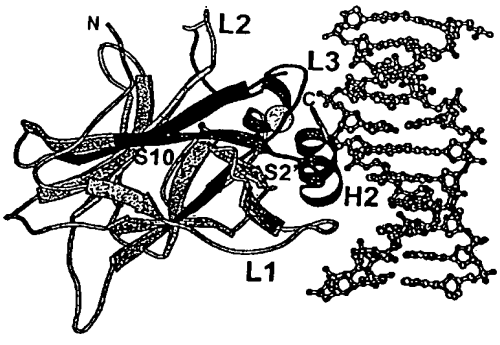
(54) Title: GLOBAL SUPPRESSORS OF P53 MUTATIONS





(57) Abstract: The transcription factor and tumor suppressor protein p53 is inactivated in many human cancers. Approximately forty percent of cancers carry large amounts of mutated full-length p53 protein with one of over 900 reported single amino acid changes in the p53 core domain that recognizes p53 DNA binding sites. The ability to restore function to these inactive p53 proteins would dramatically improve cancer therapy. We show that this goal is achievable. Using genetic strategies and p53 assays in the yeast *S. cerevisiae* and mammalian cells, we identify suppressor mutations that, in the context of the same protein, restore function to some of the most common p53 cancer mutants tested. Crystallographic studies of this general suppressor motif eludicate the structural basis of restoring integrity to the p53 core domain and lead to small compounds that stabilize p53 cancer mutants.

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